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Prevalence of Smoking in Patients with Seizures: Epilepsy vs. Psychogenic Nonepileptic Seizures

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *Smoking is the second most significant cause of early death and disability worldwide.*
- *Epilepsy and psychogenic nonepileptic seizures (PNES), also known as dissociative seizures, are 2 distinct neuropsychological conditions; they exhibit numerous similarities. There is no study investigating smoking among patients with these 2 types of seizures.*

WHAT DOES THIS STUDY ADD ON THIS TOPIC?

- *A total of 1491 patients were studied. In total, 226 patients (15.2%) reported smoking. The prevalence rate of smoking in idiopathic generalized epilepsy was 13.3% and in PNES was 21.3%; P = .01.*
- *Having PNES was significantly associated with smoking.*
- *Female sex and having a college education were inversely associated with smoking.*

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ABSTRACT

Objective: Smoking is the second most significant cause of early death and disability worldwide. Considering existing clinical and psychological differences between patients with epilepsy and psychogenic nonepileptic seizures (PNES), it was assumed that these 2 groups of patients vary in their rates of smoking. This retrospective study was based on an electronic dataset of patients with seizures.

Methods: All patients aged 20 years or older were surveyed at the outpatient epilepsy clinic of Shiraz University of Medical Sciences in Shiraz, Iran, between 2008 and 2020. Age at seizure onset, sex, and the final diagnosis were entered into the database for all patients. Other collected data included tobacco smoking (including cigarette and water-pipe as the 2 common forms of smoking).

Results: A total of 1491 patients were examined. In total, 226 patients (15.2%) reported smoking. Smoking rates were 13.3% in patients with idiopathic generalized epilepsy, 14.3% in those with focal epilepsy, and 21.3% in individuals with PNES ($P = .01$); a diagnosis of PNES was significantly linked to smoking. Female sex, younger age at the seizure onset, and having a college education were significantly inversely associated with smoking.

Conclusion: The high prevalence rate of smoking among patients with functional seizures is notable. It would be helpful to do a qualitative study on patients with functional seizures to understand why they are smoking. This can help us to understand the actual reasons behind the high prevalence rate of smoking in this population.

Keywords: Epilepsy, psychogenic, seizure, smoking, tobacco

INTRODUCTION

Epilepsy and psychogenic nonepileptic seizures (PNES) are distinct disorders; yet, they share several clinical features that may complicate differentiation. For example, both of these conditions (i.e., epilepsy and PNES) are associated with increased mortality.[1,2]While many causes (e.g., suicide, sudden

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death, underlying problems, injuries, etc.) may explain this increased mortality to some extent, the full spectrum of the reasons for premature mortality among these 2 groups of patients is not entirely clear yet. There is no study investigating mortality among patients with seizures who smoke as compared to those who do not smoke. Having said that, smoking is the second most significant risk factor for premature death and disability worldwide,[3]and it is a preventable risk factor. Based on the Global Burden of Disease Study (GBD) in 2015, the prevalence of smoking was estimated to be 25% in the world.[4] In Iran, smoking prevalence was estimated to be 13.9% according to a meta-analysis that was performed in 2013.[5]

Some studies have shown that preexisting depression or anxiety can predict later smoking behavior, whereas others have found that smoking itself may increase the risk of developing subsequent depression or anxiety.[6,7] Moreover, 1 study indicated that quitting smoking is linked to a reduction in symptoms of common mental health disorders, such as depression.[8]

On the other hand, psychiatric comorbidities (e.g., depression) are common in patients with epilepsy and even more common in those with PNES.[7] Therefore, it is plausible to assume that smoking is common among these patient populations. Globally, smoking appears to be more prevalent among individuals with epilepsy compared with the general population.[9] Furthermore, PNES has been more prevalent among those with a history of smoking.[10] It would be helpful to know the prevalence rate of smoking in patients with epilepsy and in those with PNES. This information could help public health policymakers to design tailored programs and strategies to tackle the issue of smoking, a significantly modifiable exposure, in different populations. These strategies may help reduce the risk of early death, at least to some extent.

In this study, the rate of smoking, including cigarette and water pipe, among individuals experiencing seizures (such as PNES or epilepsy) was investigated in a large data set from Iran.

As idiopathic generalized epilepsy (IGE) and focal epilepsy differ fundamentally in their specific psychiatric profiles, underlying mechanisms, and risk factors, they were placed in 2 separate groups for the study. Considering the psychological and clinical differences between patients with PNES and those with epilepsy (focal epilepsy or IGE; the 2 large groups of patients with epilepsy in adults) (e.g., different prevalence rates of depression),[11] it was hypothesized that there existhigher prevalence rates of smoking in patients with PNES compared to those with epilepsy. The patterns observed among smokers in these groups of patients were also evaluated.

MATERIAL AND METHODS

Participants and Procedures

This was a retrospective study based on an electronic dataset of patients with seizures developed over more than 12 years. All patients aged 20 years or older (at the time of diagnosis), diagnosed with focal epilepsy, IGE, or PNES in the epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 to 2020 were reviewed. The first author conducted interviews with all patients, reviewed their electroencephalogram (EEG) and brain imaging results, and confirmed the diagnosis of PNES by documenting[12] their typical episodes through video-EEG monitoring. The International League Against Epilepsy (ILAE) Classification of the Epilepsies (2017) was used for the diagnosis of patients with epilepsy.[13] Those with IGE or focal epilepsy were categorized according to a thorough clinical history, focusing on seizure semiology, and inter-ictal EEG results. Patients with multiple seizure types (e.g., PNES and epilepsy) or missing data were not included in the study. It should be clarified that, in Iran, the sale of tobacco products to anyone under the age of 18 years is prohibited and is punishable by law.[12]

Data Collection

Age at seizure onset, age at diagnosis, sex, and the ultimate diagnosis were entered into the database for all patients. Other collected data included tobacco smoking (including cigarette and water-pipe as the 2 common forms of smoking; these were not differentiated from one another), marital status (i.e., married vs. not), and education level (i.e., college vs. school vs. no education).

Statistical Analyses

Values were presented as number (percent) of subjects for categorical variables and as mean ± standard deviation for continuous variables. Data analysis was done by Pearson chi-square test, Fisher's exact test, one-way analysis of variance, and *t*-test. In the next step, variables with $P \leq .1$ were evaluated in univariate analyses in a logistic regression analysis model. Model performance was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Odds ratios (ORs) and 95% CIs were calculated with a logistic regression test. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.; Armonk, NY, USA). A *P* value of less than .05 (two-sided) was considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective study was approved by the Shiraz University of Medical Sciences Institutional Review Board (IR.SUMS.REC.1400.146, Date of Approval: May 23, 2021). The participants were informed that involvement in this study is voluntary and gave their written informed consent for the use of their data for research purposes. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

RESULTS

A total of 1491 patients were included in the study: 338 patients with IGE, 918 individuals with focal epilepsy, and 235 individuals with PNES. The mean age of the patients was 32 ± 11 years old (range: 20-90 years; median 29 years; and interquartile range 13 years). Age at diagnosis was higher in patients with focal epilepsy compared to the other groups ($P = .001$; 33.5 ± 11.7 in focal epilepsy, 30.9 ± 9 in PNES, and 27.5 ± 7.9 in IGE). There were 719 men (48.2%) and 772 women (51.8%). Among patients with IGE, 133 (39.3%) were men and 205 (60.6%) were women. In the focal epilepsy group, 512 (55.8%) were men and 406 (44.2%) were women, while among those with PNES, 74 (31.5%) were men and 161 (68.5%) were women. Tobacco smoking was reported by 71 women (9.2%) and 155 men (21.6%) Overall, 226 patients (15.2%; 95% CI: 13.4-17.1) reported smoking. The prevalence rate of smoking was 13.3% (95% CI: 9.7-16.9; 45 of 338) in patients with IGE, 14.3% (95% CI: 12.0-16.5; 131 of 918) in those with focal epilepsy, and 21.3% (95% CI: 16.0-26.5; 50 of 235) in individuals with PNES; the difference was was statistically significant ($P = .01$; $df = 2$; Pearson chi-square test).

Table 1 displays the factors associated with smoking in univariate analyses. Patients who smoked, compared with those who did not, had an older age at seizure onset, were more frequently male (69% vs. 46%), were more often married at diagnosis (67% vs. 51%), and

Table 1. Factors Associated with Smoking in Univariate Analyses

	Smoking (N = 226)	Not Smoking (N = 1265)	*P*	*df*; test
Sex ratio (female: male)	0.46 (71: 155)	1.24 (701: 564)	0.0001	1; FE
Age at diagnosis, years (SD)	35 (12)	31 (10)	0.0001	1489; *t*-test
Age at onset, years (SD)	25 (14)	20 (13)	0.0001	1489; i-test
Family history of seizures (%)	57 (25)	325 (26)	0.93	1; FE
Marital status (married) (%)	151 (67)	645 (51)	0.0001	1; FE
Education (none:school:ollege)	24:158:44	121:790:354	0.02	2; PCS
Diagnosis (IGE, focal epilepsy, PNES)	45, 131, 50	293, 787, 185	0.016	2; PCS

df, degree of freedom; FE, Fisher's exact test; IGE, idiopathic generalized epilepsy; PCS, Pearson chi-square test; PNES, psychogenic nonepileptic seizures.

less often had a college education (19% vs. 28%). Variables with a *P* value ≤ .1 (including diagnosis, sex, age at seizure onset, age at diagnosis, marital status, and education as covariates) were then included in a regression analysis model to examine the association of each variable with smoking (the dependent variable).

The binary logistic regression analysis produced a significant model (*P* = .0001), accurately predicting 84.6% of patients who reported smoking. The Hosmer–Lemeshow goodness-of-fit test indicated an adequate model fit (*P* = .621). Table 2 presents the factors associated with smoking identified in the regression model. Being married and having a diagnosis of PNES were significantly associated with smoking. Female sex, younger age at seizure onset, and having a college education were significantly inversely associated with smoking.

In those with IGE, 166 (49.1%) were single, 167 (49.4%) were married, and 5 (1.5%) were divorced; in patients with focal epilepsy, 414 (45.1%) were single, 493 (53.7%) were married, 10 (1.1%) were divorced, and 1 was a widower. In the PNES group, 90 (38.3%) were single, 136 (57.9%) were married, 7 (3%) were divorced, and 2 were widowers (*P* = .013). Regarding educational status, in those with IGE, 14 (4.1%) had no education, 202 (59.8%) had completed school, and 122 (36.1%) were college graduates. In patients with focal epilepsy, 103 (11.2%) had no education, 596 (64.9%) had completed school, and 219 (23.9%) were college graduates. In the PNES, 28 (11.9%) had no education, 150 (63.8%) had completed school, and 57 (24.3%) were college graduates (*P* < .0001).

DISCUSSION

In the current study, it was observed that almost 1 in 7 patients with seizures reported smoking; this rate is similar to the prevalence of smoking in the general population in Iran (13.9%).[5,14] Significantly, more patients with PNES (21.3%) reported smoking compared to that by patients with epilepsy (14.0%), with an OR of 2.1. In other words, the prevalence rate of smoking in patients with epilepsy was very similar to that in the general population, while this rate was significantly higher among patients with PNES. A study from the United States showed that smoking was more common among adults with epilepsy (24.9%) compared with those without epilepsy (16.6%).[15]Another study showed that the prevalence of smoking in patients with epilepsy was 32.1%, whereas, during the same period, the prevalence of smoking in the general population of French-speaking Switzerland was 19.0%.[16]The observed differences between these studies are probably due to the existing socio-economic and cultural differences between the nations.[17] In spite of these differences, these prevalence rates of smoking among populations with epilepsy are alarming. Healthcare professionals and social service providers working with individuals with epilepsy should encourage the use of smoking cessation resources to support quitting efforts and decrease the risk of smoking-related illnesses and mortality.[15] It is noteworthy to mention that smokers with epilepsy do not appear to differ significantly from smokers without epilepsy with regard to smoking-related behaviors, and may therefore benefit from current evidence-based treatments for smoking cessation (if they are not contraindicated in people with epilepsy).[18] Cigarette smoking presents a complex challenge in individuals with epilepsy, as both nicotine and tobacco smoke can exert proconvulsant as well as anticonvulsant effects, being demonstrated in various animal models and human studies.[15,19,20]

Table 2. Factors Associated with Smoking in a Regression Analysis Model

	Odds Ratio	95% CI	*P*
Sex (female)	0.30	0.22-0.42	.0001
Age at seizure onset	0.97	0.96-0.99	.004
Married	1.56	1.10-2.21	.01
College education vs. none	0.64	0.44-0.92	.01
PNES vs. IGE	2.12	1.42-3.18	.0001

Age at diagnosis (*P* = 0.88) and type of epilepsy (focal epilepsy vs. IGE (*P* = .14)) were not associated with smoking.
IGE, idiopathic generalized epilepsy; PNES, psychogenic nonepileptic seizures.

A study of women found that current smoking was linked to a higher risk of seizures compared to never smoking (RR 2.60, 95% CI 1.53-4.42). In addition, while past smoking did not increase the risk of seizure, it was seen to be associated with elevated risk of epilepsy (RR 1.46, 95% CI 1.01-2.12).[21]

More research is required to clarify the connections between seizure control status, smoking, and quitting smoking in individuals with epilepsy. The observed higher prevalence rate of smoking among patients with PNES (compared with that in patients with epilepsy and also the general population) is an important finding of the current study and is really alarming. First, smoking is an important risk factor for early death and disability;[3] it is a preventable risk factor. Second, smoking may have a bidirectional relationship with psychiatric problems;[6,22]and, psychiatric comorbidities are common in patients with PNES (even more common than that in patients with epilepsy).[11] Finally, it is noteworthy to mention that patients with PNES frequently lack healthy methods for coping and stress management.[21] Whether smoking may serve as a coping behavior in patients with PNES requires further investigation in future studies. A negative

association also exists between smoking and quality of life, with the strength of this relationship increasing with the number of cigarettes smoked.[23, 24] Quality of life is an important concern in patients with seizures (epilepsy and PNES). Generally speaking, smoking cessation significantly improves the quality of life.[24]

Smoking activates and changes various brain networks and regions. The cognitive control network, salience network, and dopaminergic reward network are involved in dependence on many substances, including tobacco (smoking).[25-27] For example, cigarette smoking may lead to persistent alterations of brain activity and connectivity in the anterior insula and anterior cingulate.[26] On the other hand, there is growing evidence of abnormal brain connectivity in patients with PNES.[28,29] Abnormal functional brain connectivity between emotion-processing regions and areas responsible for executive control and cognitive function, along with altered connections of the anterior cingulate cortex, may contribute to the pathophysiology of PNES.[29] Although the present study (and similar cross-sectional or retrospective studies) cannot establish a cause-and-effect relationship between smoking and neuropsychiatric conditions, this remains an important avenue for future research. Studying the brain networks involved in smoking and PNES may help clarify the mechanisms underlying PNES and support the development of more effective treatment strategies for both conditions.

In the current study, being married was significantly linked to smoking, while female sex, younger age at the seizure onset, and having a college education were significantly inversely associated with smoking. The reasons behind these associations are not clear yet and should be investigated in future studies. In a previous systematic review of the risk factors of smoking among Saudi adolescents, social influence of others and a low academic performance were the most commonly reported risk factors for smoking.[30] In another study of the association between smoking and income level, the authors concluded that cigarette smoking was significantly associated with a lower income.[31] Finally, a study from the United States showed that lower educational attainment was associated with increased smoking prevalence.[32] Knowledge of the risk factors for smoking and also protective factors against smoking in various populations could help public health policy-makers to design goal-oriented and tailored programs to tackle the global issue of smoking more efficiently.

Limitations

This series was conducted at a specialist center, so it may not capture the entire range of PNES or epilepsy patients; there is a chance of selection bias. Additionally, potential psychiatric comorbidities were not explored in the patients. Patients were also not matched according to their age among groups. This study is also limited by its retrospective design and dependence on self-reported smoking data, which may introduce recall bias and affect the accuracy of the reported smoking status. Smoking status was assessed only as present or absent, and the frequency of smoking was not evaluated. Age at diagnosis and age at seizure onset were both included in the model, which may introduce multicollinearity.

Conclusion

The high prevalence rate of smoking among patients with functional seizures is alarming. It would be helpful to do a qualitative study on patients with functional seizures to understand why they are smoking. This can help us to understand the actual reasons behind the high prevalence rate of smoking in this population.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no artificial intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Shiraz University of Medical Sciences (Approval no: IR.SUMS.REC.1400.146, Date: May 23,2021).

Informed Consent: Written informed consent was obtained from participants who participated in this study.

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